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Research Article

THE NEW THOUGHTS IN DRUG RESEARCH TO PREVENT TERATOGENCITY

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A B S T R A C T

In late 1950's and early 1960's the drug Thalidomide caused an estimated 10,000 birth defects and thousands of fetal deaths world wide. The affected babies typically suffered from phocomelia, a failure of the limbs to develop. These unfortunate babies were cruelly referred to as "Flipper babies".

This drug formerly used as a sedative, but with drawn in the early 1960's after it was found to cause congenital malformation or absence of limbs in children whose mothers took the drug during early pregnancy. Thalidomide is a sedative that used to be prescribed to treat anxiety, tension, gastritis and insomnia. It was also used to relieve morning sickness in pregnant women.

Man today living in a world created by him that is becoming more and more hostile every day owing to pollution.The subtle effect of Thalodomide tragedy resulting in phocomalia, apoda etc in the offspring led to untold miseries. There are similar good number of cases of fetal deaths, still births, terratogenices etc.in the young ones of mothers exposed to toxic ants like pesticides, radiation, heavy metal etc. Can we save innocent lives was the question that was prompted me to choose the topic of my research. Doing research with human subjects is illegal and unethical.So I have to go non-human material which stimulates human being. To study the long term effects of the toxicants on the fetal development.Rats have 21, rabbits 30, dog has 60 days gestation period. Where as gestation period is long as in case of sheep, monkeys, elephants, they are not available because of cost procurement and maintenance.So in this situation scorpion comes handy, cheap, available, viable and reliable, with viviparity and long gestation period of little over 10 months.Hence scorpion was chosen as a medical research model. It is found in my research, by administering the ch elating agents like BAL to the heavy metal exposed mothers the adverse effects of Mercury and Lead on both mother and the fetus could be elevated.

INTRODUCTION

Can you trust all medicines in pharmacy? Are all the drugs tested on experimental animals? Is it sin or boon to conduct drug tests on animals? Drug discovery is the process by which new medications are discovered. Modern drug discovery involves the identification of screening hits, medicinal chemistry and optimization of those hits to increase the affinity, selectivity (to reduce the potential of side effects), efficacy/potency, metabolic stability (to increase the half-life), and oral bio-availability. Once a compound that fulfills all of these requirements has been identified, it will begin the process of drug development prior to clinical trials.

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Most of the drugs are tested on less gestation period animals like mice, rats, rabbits, guinea pigs. It is very difficult to do research work on long gestation period animals like monkeys, goats, buffalos etc.To do research on human is illegal, ultra wire. The drug that is safe to animals may not be suitable to human. Most of the drugs in the pipeline have failed in clinical trials. Tempting situations and impulsive decisions will ruin personality. Narrow Therapeutic Drugs are considered "narrow therapeutic index" (NTI) drugs. That means the safe dose that works is very close to a toxic dose. This is why it is crucial that patients get a reliable dose that poses no risk of quality control problems or dosage variability.

Many people feel that the FDA's standards on such medications has historically been too lax. That is why some physicians specify the brand name product for NTI medications. (The people's pharmacy) The Animals and human get many of the same illnesses. Medical research with

animals is one type of medical research, but other types include experiments with cells and chemicals and simulations on computers. Animal research usually describes research involving vertebrates, such as cats, mice, frogs, pigs, and primates. All medical research is carefully planned, and this includes medical research with animals. Under federal law, all animals must be treated humanely and undergo the least distress possible. Medical research with animals saves Lives. Dog- discovery of insulin, monkey-- polio vaccine, mouse-- rabies vaccine, pig ---skin grafts for burn victims and computer-assisted tomography (CAT) scans, rabbit-- corneal transplants, rat--carcinogen screening. Medical research that helps animals discovery how it helps animals research on viruses, for example dog--- parvo virus vaccine. In late 1950's and early 1960's the drug Thalidomide caused an estimated 10,000 birth defects and thousands of fetal deaths worldwide. The affected babies typically suffered from phocomelia, a failure of the limbs to develop. These unfortunate babies were cruelly referred to as "Flipper babies".This drug formerly used as a sedative, but with drawn in the early 1960's after it was found to cause congenital malformation or absence of limbs in children whose mothers took the drug during early pregnancy. Thalidomide is a sedative that used to be prescribed to treat anxiety, tension, gastritis and insomnia.It was also used to relieve morning sickness in pregnant women. Man today living in a world created by him that is becoming more and more hostile every day owing to pollution. The subtle effect of Thalidomide tragedy resulting in phocomelia, apoda etc. in the offspring led to untold miseries. There are similar good number of cases of fetal deaths, still births, teratogenices etc. the young ones of mothers exposed to toxic ants like pesticides, radiation, heavy metal etc. Can we save innocent lives was the question that was prompted me to choose the topic of my research. Doing research with human subjects is illegal and unethical. So I have to go non-human material which stimulates human being. To study the long term effects of the toxic-ants on the fetal development. Rats have 21, rabbits 30, dog has 60 days gestation period. Whereas gestation period is long as in case of sheep, monkeys, elephants, they are not available because of cost procurement and maintenance. So in this situation scorpion comes handy, cheap, available, viable and reliable, with viviparity and long gestation period .All scorpions have a long gestation period. It goes from several months to a year and a half, depending on species. The young scorpions develop as an embryo in the mother's uterus. During this time, the embryo gets food from his mother. Hence scorpion was chosen as a medical research model. It is found in my research; by administering the chelating agents like Dimercaprol (BAL) to the heavy metal exposed mothers the adverse effects of Mercury and Lead on both mother and the fetus could be elevated. Objectives: The known drugs that more or less cause teretogenecity , Methamphetamine,Thalidomide, Isotretinoin (used in treatment of cystic acne), Methotrexate (Folic acid antagonistic) Azathioprine (renal transplant), Cyclophosphamide (infant malformation), Chloroquine (cochlea vestibule perisis) Phenytoin, valproic acid, carbamazine (cleft palate,congenital heart disease), Lamitrigine (increased. cyclophosphamide is teratogenic and contraindicated in pregnant women (pregnancy category D) except for life-threatening circumstances in the mother. Additional relative contraindications to the use of cyclophosphamide include lactation, active infection, neutropenia or bladder toxicity(1) Cyclophosphamide is a pregnancy category D drug and causes birth defects. First trimester exposure to cyclophosphamide for the treatment of cance or lupus displays a pattern of anomalies labeled "cyclophosphamide embryopathy," including growth restriction, ear and facial abnormalities, absence of digits and hypoplastic limbs(2)

Carbamazepine (CBZ), sold under the tradename Tegretol among others, is a medicationused primarily in the treatment of epilepsy and neuropathic pain. Common side effects include nausea and drowsiness. Serious side effects may include skin rashes, decreased bone function, suicidal thoughts, or confusion. It should not be used in those with a history of bone marrow problems. Use during pregnancy may cause harm to the baby; however stopping it in pregnant women with seizures is not recommended. Its use during breastfeeding is not recommended. Care should be taken in those with either kidney or liver problems(3)

Phenytoin (PHT), sold under the brand name Dilantin among others,[1] is an anti-seizure medication(4) It is useful for the prevention of tonic-clonic seizures and partial seizures, but not absence seizures. The intravenous form is used for status epilepticus that does not improve with benzodiazepine. It may also be used for certain heart arrhythmias or neuropathic pain. It can be taken intravenously or by mouth. (4) The intravenous form generally begins working within 30 minutes and is effective for 24 hours.Common side effects include nausea, stomach pain, loss of appetite, poor coordination, increased hair growth, and enlargement of the gums. Potentially serious side effects include sleepiness, self harm, liver problems, bone marrow suppression, low blood pressure, and toxic epidermal necrolysis. There is evidence that use during pregnancy results in abnormalities in the baby(5)

Phenytoin is a known teratogen. The syndrome consists of craniofacial anomalies (broad nasal bridge, cleft lip and palate, smaller than normal head) and a mild form of mental retardation (average IQ=71)(6) This syndrome resembles the well-described Fetal Alcohol Syndrome(7) and has also been called the "fetal hydantoin syndrome".

Experimental research with animals is usually conducted in universities, medical schools, pharmaceutical companies, defense establishments and commercial facilities that provide animal-testing services to industry. (8) By one estimate the number of mice and rats used in the United States alone in 2001 was 80 million. (9) Mice, rats, fish, amphibians and reptiles together account for over 85% of research animals(10). Insulin was first isolated from dogs in 1922, and revolutionized the treatment of diabetes. (11) antibiotic treatments and vaccines for leprosy were developed using armadillos (12), then given to humans(13). The ability of humans to change the genetics of animals took a large step forwards in 1974 when Rudolf was able to produce the first transigenic, by integrating DNA from the S V.40 virus into the genome of mice(14).

This genetic research progressed rapidly and, in 1996,Dolly sheep was born, the first mammal to be cloned from an adult cell(15) However, in response to the Elexir Sulphonamide disater of 1937 in which the eponymous drug killed more than 100 users, the U.S. congress passed laws that required safety testing of drugs on animals before they could be

marketed. Other countries enacted similar legislation. (16) In the 1960s, in reaction to the Thalidomide tragedy, further laws were passed requiring safety testing on pregnant animals before a drug can be sold(17).

The most frequently used invertebrate species are Drosophila melanogaster, a fruit fly, and coenorhabditis elegansa nematode worm. In the case of *C. elegans*, the worm's body is completely transparent and the precise lineage of all the organism's cells is known, (18) while studies in the fly *D. melanogaster* can use an amazing array of genetic tools. (19)
Major advances and discoveries-

Animals and human get many of the same illnesses. Medical research with animals is one type of medical research, but other types include experiments with cells and chemicals and simulations on computers. Animal research usually describes research involving vertebrates, such as cats, mice, frogs, pigs, and primates. All medical research is carefully planned, and this includes medical research with animals. Under federal law, all animals must be treated humanely and undergo the least distress possible.

Medical research with animals saves Lives. Dog- discovery of insulin, monkey-- polio vaccine, mouse-- rabies vaccine, pig ---skin grafts for burn victims and computer-assisted tomography (CAT) scans, rabbit-- corneal transplants, rat--carcinogen screening.(National institute of health) (NIH).

Nearly 60 years ago thalidomide was prescribed to treat morning sickness in pregnant women. What followed was the biggest man-made medical disaster ever, where over 10,000 children were born with a range of severe and debilitating malformations.(21)

History and mechanisms

The subtle effect of Thalidomide tragedy resulting in phocomalia, apoda etc in the offspring led to untold miseries. The drug Thalidomide caused an estimated 10,000 birth defects and thousands of fetal deaths worldwide. The affected babies typically suffered from phocomelia, a failure of the limbs to develop. These unfortunate babies were cruelly referred to as "Flipper babies". This drug formerly used as a sedative, but with drawn in the early 1960's after it was found to cause congenital malformation or absence of limbs in children whose mothers took the drug during early pregnancy. Thalidomide is a sedative that used to be prescribed to treat anxiety, tension, gastritis and insomnia. It was also used to relieve morning sickness in pregnant women.

There are similar good number of cases of fetal deaths, still births, terratogenices etc. The young ones of mothers exposed to toxic ants like pesticides, radiation, heavy metal etc. Can we save innocent lives growing in the wombs of the mother from becoming the victims of hostile environment that cannot avoid. This was the question that was prompted me to choose the topic of my research.

Doing research with human subjects is illegal and unethical. So I have to go non-human material which stimulates human being. Viviparity is common among est mammals but not many provide long gestation period.

Significant GAP In Research

There are two major challenges, designing a drug that could potentially target the multiple path ways involved and developing models that would help rapid screening of potential drugs. Most drugs in the pipeline have failed in clinical trails.

Current Debate

As the experimentation on animals increased, especially the practice of vivisection, so did criticism and controversy. In 1655, the advocate of Galenic physiology Edmund O'Meara said that "the miserable torture of vivisection places the body in an unnatural state"(22) O'Meara and others argued that animal physiology could be affected by pain during vivisection, rendering results unreliable. There were also objections on an ethical basis, contending that the benefit to humans did not justify the harm to animals. Early objections to animal testing also came from another angle—many people believed that animals were inferior to humans and so different that results from animals could not be applied to humans.

On the other side of the debate, those in favor of animal testing held that experiments on animals were necessary to advance medical and biological knowledge. Claude Bernard—who is sometimes known as the "prince of vivisectors"(23)and the father of physiology, and whose wife, Marie Françoise Martin, founded the first anti-vivisection society in France in 1883(24)—famously wrote in 1865 that "the science of life is a superb and dazzlingly lighted hall which may be reached only by passing through a long and ghastly kitchen"(25) Arguing that "experiments on animals ... are entirely conclusive for the toxicology and hygiene of man...the effects of these substances are the same on man as on animals, save for differences in degree"(29) Bernard established animal experimentation as part of the standard scientific method(26)

In 1896, the physiologist and physician Dr. Walter B. Cannon said "The antivivisectionists are the second of the two types Theodore Roosevelt described when he said, 'Common sense without conscience may lead to crime, but conscience without common sense may lead to folly, which is the handmaiden of crime.(27) These divisions between pro- and anti- animal testing groups first came to public attention during the Brown Do affair in the early 1900s, when hundreds of medical students clashed with anti-vivisectionists and police over a memorial to a vivisected dog(28)

-- To study the long term effects of the toxic-ants on the fetal development.Rats have 21, rabbits 30, dog has 60 days gestation period. Where as gestation period is long as in case of sheep, horses, monkeys, elephants, they are not available because of cost procurement and maintenance .

So in this situation scorpion comes handy,cheap,available, viable and reliable, with viviparity and long gestation period .All scorpions have a long gestation period. It goes from several months to a year and a half, depending on species. The young scorpions develop as an embryo in the mother's uterus. During this time, the embryo gets food from his mother. Hence scorpion was chosen as a medical research model. It is not enough, that we discover that the polutant effects the mother and the fetus. In several ways but not to overcome these effects in more important to live in the toxic circumstances with out toxic impact.

Ideas Where Research Go Next

1. Scorpion is easy to handle and observe.
2.
3. Very economical compared with the expense of larger animals.

Have longest gestation period .More than 11 months It comes under the small animal category, hence comes under the purview of local ethical committee. Larger animals require an additional clearance from the central ethical committee clearance which is a time-consuming process with stringent rules.

4.

5. The mandatory rearing facilities for ethical clearance for surgical procedures on larger animals are very elaborate and expensive, generally only within the capacity of central animal research facilities. It is found in my research, by administering the chelating agents like Dimercaprol (BAL) to the heavy metal exposed mothers the adverse effects of Mercury and Lead on both mother and the fetus could be elevated.

6.

Extrapolating to humans, it is possible to protection to the fetus of industrial workers by monitoring the heavy metal lode periodically and administering the appropriate dose of antidote. Of course, much work on these lines is needed before we can carry it over.

This invertebrate offer some advantages over vertebrates in animal testing being with longest gestation period .The long term toxicity can be studied. Long term drug action, teratogenic effects can be studied. If I am permitted to suggest, i may say that there is enormous scope for us in the medical field to contribute to science and human welfare by taking research of this type and doing collaborative work with other professors of different universities.

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